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10/551,882	01/15/2007	Achim Harder	Le A 36379	6821

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EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
11/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,882	HARDER ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8 are pending. Receipt and consideration of Applicants' amended claim set and remarks/arguments mailed on July 16th 2008 is acknowledged. Claims 1 is amended and new claims 2-8 were added.

Applicants' arguments, filed 07/16/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

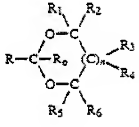
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Rejection

This rejection is necessitated by the newly submitted claims filed on 07/16/2008.

Claims 1-5 and 8 of the instant application are rejected under 35 U.S.C. 103(a) as unpatentable over Samour et al. (US 4861764, previously submitted) in view of Pieasecki et al (PL 175837, abstract) and Cooper et al (US 4557934)

Samour teaches compounds having the general formula



whereby n=2 or 3, R = C5-C11, R_0, R_1, R_2, R_3, R_4, R_5, and R_6, are each independently selected from hydrogen and C.sub.1 to C.sub.18 aliphatic groups, preferably alkyl, alkenyl, and the halo, hydroxy, carboxy, carboxamide and carboalkoxy substituted forms thereof, with at least one of said R's an alkyl or alkenyl group of C.sub.4 to C.sub.18 and n=0 or 1 (col.2, lines 33-48); Samour teaches the preparation methods for 2-n-nonyl-1,3 dioxolane and 2-n-nonyl-1,3, dioxane (col.4, examples III and col.7 example XIII respectively). Samour also describes 1,3-dioxacyclopentanes or 1, 3-dioxacyclohexanes as effective in enhancing the transport of a large number of higher-dose poorly-absorbed drugs through the skin (column 2, lines 25-33) and teaches that these compounds may be applied in conjunction with any agent it is desired to transdermally administer to humans and animals as in admixture therewith

(col.3, lines 45-47). Samour additionally teaches therapeutic compositions of the compounds of his invention for transdermal administration (column 10, claims 1-12). Samour teaches compounds 2-nonyl-1,3-dioxolane and 2-nonyl-1,3-dioxan. Absence of evidence to contrary, the penetration enhancing effect of the compounds taught by Samour may be equal or better than the penetration enhancing effect of instantly taught compounds. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of obviousness has been established In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

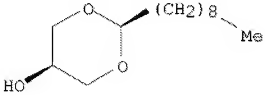
Samour does not teach co-administration of the pharmaceutically active substance with at least two penetration enhancing compounds one of which is eithr compound 1: 2-nonyl- 1,3-dioxolane-4-methanolor compound 2: 2-nonyl-1,3-dioxan-5-ol. Samour also does not teach the specifics types of pharmaceutically active substance (fluroquinolone or mebendazole) which is to be co-administered with the penetration enhancers.

However, Piasecki teaches diasteroisomers of cyclic glycerol acetals (I) and their trans-isomers (II) intermediates for the manufacture of surfactants by transacetalization of 4 component mixtures for e.g. Piescki teaches a mixture comprising cis-2-nonyhl-5-hydroxy-1,3-dioxane (V) , trans-2-nonyhl-5-hydroxy-1,3-

dioxane (VI), cis -2-nonyl-4-hydroxymethyl-1,3-dioxolane and trans-2-nonyl-4-hydroxymethyl-1,3-dioxolane in the presence of p-MeC6H4SO3H as catalyst for 2 days at ambient temperature and crystals were separated, filtered, dried and distilled to give cis-2-nonyl-5-hydroxy-1, 3-dioxane (Abstract) Piasecki teaches the compound which is the same compound as that claimed in instant claim 1 and teaches the compound to be useful as surfactant.

CN 1,3-Dioxan-5-ol, 2-nonyl-, cis- (CA INDEX NAME)

Relative stereochemistry.



Cooper teaches compositions which enhance the utility of certain pharmaceutically active agents by effectively delivering these agents through the integument (col.1, lines 6-10). Cooper teaches that penetration enhancing efficacy of 1-dodecyl-azacycloheptan-2-one (Azone) which have been described as being useful in aiding in the penetration of certain anti-bacterial agents, antibiotics, steroids, anti-fungal agents etc can be significantly improved when it is used in a select binary combination with certain other penetration enhancing agents (col. 2, lines 51-62). Cooper teaches specifically that a binary penetration system comprising Azone in combination with a diol, certain other n-substituted-alkyl-azacycloalkyl-2-ones, or mixtures thereof, consistently and dramatically demonstrates improved topical delivery of certain

pharmaceutically-active agents, such as steroids, when the second component is used at specific levels and when the components of the binary combinations are present at specific ratios (col.2, line 58 – col.3, line 2). Cooper additionally teaches that certain binary skin penetration systems can increase the disorder of lipids in the skin. By so increasing the disorder of the lipid portion of the cell-envelope in the stratum corneum, the lipid packing of the cells can be disrupted. This disruption allows certain pharmaceutically active agents to pass through the stratum corneum. This discovery has been confirmed by differential scanning calorimetry, indicating that certain binary skin penetration enhancement systems eliminate the Tm-2 peak associated with melting of cell-envelope lipids. (col. 3, lines 39-48). Cooper teaches the compositions with the binary mixture wherein the ratio of weight of the two penetration enhancing agents is from about 1:5 to about 100:1 (col. 35, claim 2). Cooper also teaches a host of pharmaceutically-active agents which are useful in the composition of his invention which includes antimicrobials, antiameobic , antiprotozoan , anthelmentic, and antifungal agents ((col. 9, lines 55-60). Finally Cooper provides examples of compositions comprising the active pharmaceutical and the binary penetration enhancing systems (col.26, line 45- col.27, line 38).

In view of the foregoing references, the instantly claimed method to improve permeation of a pharmaceutically active substance across cell barrier with at least two penetration enhancing compounds with one of the compounds being either compound 1: 2-nonyl- 1,3-dioxolane-4-methanol or compound 2: 2-nonyl-1,3-dioxan-5-ol would have been prima facia obvious to one of ordinary skill in the art at the time the

invention was made. Samour teaches compounds which are encompassed by the instant claim1 as penetration enhancers and teaches compounds,2-nonyl-1,3-dioxolane and 2-nonyl-1,3-dioxan which are structurally similar to the claimed compounds 1 and 2 except for the additional, methanol and hydroxy groups attached to the heterocyclic ring respectively. Piasecki teaches instantly claimed compound 2 (: 2-nonyl-1,3-dioxan-5-ol) and its possible use as a surfactant. Cooper teaches that administration of binary permeation enhancers results in enhanced penetration of the active substances. Cooper additionally teaches the advantages of using a binary skin penetration systems which provides motivation to one of ordinary skilled in the art to combine the three references and use at least one of the compounds claimed by Samour and : 2-nonyl-1,3-dioxan-5-ol taught by Piasecki for enhancing penetration of a pharmaceutical. Moreover, It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 U.S.P.Q. 186, 188 (CCPA 1960). Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that two individually known penetration enhancers would, when combined, provide a third composition also useful enhancing penetration of drugs flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (e.g. unexpected results) to

rebut this natural presumption. Further, it is clear from the prior art that compounds encompassed by the structure of instant claim 1 are penetration enhancers. There would be a reasonable expectation of success that the compound disclosed in Samour would have the same properties and function as that of the instant application since the compounds have similar structures. A prima facie case of obviousness may be made when chemical compounds have very close structural similarities and/or similar utilities. "An obviousness rejection based on similarity in chemical structure and/or function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). Accordingly with regards to instant claim 8, one of ordinary skill in the art would be motivated to combine compound 2 (taught by Piasecki) and compound 1, (structurally similar compound taught by Samour) would have been obvious to one of ordinary skill in the art as, with regards to the limitation of the ratio of the two drugs, the references above does not specifically teach the ratio claimed in instant claims 8. However, it would be within the skill of an ordinary artisan to be able to modify the weight ratio of either of the two drugs in order to obtain optimal penetration enhancement of the pharmaceutical compound. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

One skilled in the art would have been imbued with at least a reasonable expectation that combination of two or more compounds of the same would further improve the penetration capability of the cell barrier.

Claim 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samour et al. (US 4861764, previously submitted) in view of Piasecki et al (PL 175837, abstract) and Cooper et al (US 4557934) as applied to claims 1-6 and 8 and above, and further in view of Grasela et al (US 5837289)

Samour, Piasecki and Cooper teach as discussed supra and are applied here in the same manner. The cited references do not teach the pharmaceutically active substance wherein in the antibiotic is a fluoroquinolone and the antiparasitic compound is mebendazole.

However Grasela teaches the use of two separate penetration enhancers of defined function which provides rapid but controllable separation of medication from a cream and its penetration into and within or through the skin (col.3, lines 33-38). The basic composition of penetration enhancer taught by Grasela is a mixture of an organogel and a drug releasing agent (col.5, lines 46-48). Grasela teaches that a wide variety of drugs may be transported by his method (col.8,lines 11-12). Among various drugs which can be successfully incorporated into his invention, Grasela exemplifies fluoroquinolones under the broader antibacterial category (col.11, line 41) and mebendazole under the anthelmentic category (col.12, line 49).

Therefore, it would have been *prima facia* obvious to one of ordinary skilled in the art to combine the teachings of the cited references above and use penetration enhancers in combination with antibacterials such as fluoroquinolones and antihelmentics such as mebendazole . Cooper teaches the use a binary penetration system comprising Azone in combination with a diol, certain other n-substituted-alkyl-azacycloalkyl-2-ones, or mixtures thereof to enhance the delivery of antibacterial and anthelmentic and Grasela specifically teaches fluoroquinolone and mebendazole as examples of a broad catagory of antibacterials and anthelmentic whose penetration can be enhanced with his formulation . Accordingly, use of binary pentration enhancers to increase bioavailability of antibacterial and antiprotozol drugs such as fluoroquinolone and mebendazole was well known in the art. Hence one of ordinary skill in the art would have been motivated to test well known antibacterial such as fluoroquinolone and well known anthelmentic such as mebendazole with the penetration enhancers taught by Samour and Piasecki with a reasonable expectation of success that such a penetration enhancer would improve the bioavailability of the pharmaceutical compounds.

Response to applicant's arguments filed on July 16th 2008:

In light of the new grounds of rejection above, the arguments submitted on 07/16/2008 which was for the previously submitted rejection is moot.

Conclusion

Claims 1-8 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614